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Infusion of calcium and magnesium for oxaliplatin-induced sensory neurotoxicity in colorectal cancer: A systematic review and meta-analysis

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Abstract ***Background:*** It is hypothesised that infusion of calcium and magnesium (Ca/Mg) can reduce the occurrence of oxaliplatin-related sensory neurotoxicity. However, more recent data have drawn a controversial picture concerning this topic.

Methods: A comprehensive literature search was performed using Medline, Embase, Cochrane Library and Google Scholar database up to 1st August 2011. Keywords for the search were: calcium, magnesium and oxaliplatin. The odd ratio (OR) for neurotoxicity and relative risk (RR) for tumour response rate were calculated.

Results: Seven studies (four randomised controlled trials (RCTs) and three cohorts) including a total of 1238 participants met our criteria. Meta-analysis of three RCT studies that reported in National Cancer Institute-Common Toxicity Criteria (NCE-CTC) showed that OR for neurotoxicity of Grade $\geqslant 2$ was not significant (OR 0.47; 95% confidence interval (CI) 0.22–1.00, *P* homogeneity = .729). The OR was also not significant in All Grades (OR 3.15, 0.32–31.35, *P* homogeneity = .952) and Grade 3 subgroup (OR 1.64, 0.30–9.00, *P* homogeneity = .656). No statistically significant difference was observed in RR for tumour response rate. (RR = 0.91, 0.78–1.06, *P* homogeneity = .33)

Conclusions: This meta-analysis does not support the hypothesis that infusion of Ca/Mg reduces the occurrence of neurotoxicity in oxaliplatin-treated patients with colorectal cancer measuring with NCE-CTC criteria. On the other hand, our results support the hypothesis that administrations of Ca/Mg do not impair the efficacy of oxaliplatin-based chemotherapy. However, large-scale randomised, controlled clinical trials will be required to confirm these hypotheses.

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1. Introduction

Oxaliplatin, a third generation platinum compound, is a component of the FOLFOX regimen (oxaliplatin + 5-fluorouracil + leucovorin), which has been considered a standard adjuvant treatment for colorectal cancer (CRC).[1] Recently a phase III European trial, MOSAIC (Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer), has confirmed that FOLFOX regimen improves the adjuvant treatment of colon cancer.[2] Unfortunately, this platinum-containing regimen frequently induces peripheral sensory neurotoxicity, which often prevents patients from receiving oxaliplatin chemotherapy. Neurotoxicity associated with oxaliplatin often produces two clinically distinct syndromes: a transient, acute syndrome that appears during, or shortly after, administration of oxaliplatin and usually disappears within 7 days and a dose-limiting, cumulative sensory neuropathy.[3]

One of the specific strategies for prevention and management of oxaliplatin-induced neurotoxicity was administration of calcium and magnesium (Ca/Mg) solutions before and after oxaliplatin treatment. It is hypothesised that the extracellular calcium could bind within the pore of the sodium channel and subsequently facilitates the closure of sodium channel. And the increased rate of closing of sodium channel may lead to decreased neuronal hyperexcitability.[4] In 2004, Gamelin et al. published a retrospective study including 161 patients with advanced colorectal cancer and concluded that infusion of Ca/Mg can reliably reduce the occurrence of oxaliplatin-related cumulative sensory neurotoxicity.[5]

However, in 2007, the prospective CONcePT study reported that infusion of Ca/Mg negatively influenced the clinical efficacy of oxaliplatin.[6] Although the result of the CONcePT trial was later refuted by a subsequent independent analysis of CT scans from patients in this trial,[7] it had caused at least three relevant published studies[8–10] terminated prematurely. In the other hand, more recent studies have reported inconclusive results in this regard. This review was designed to assess existing evidence concerning the clinical effectiveness of administration of Ca/Mg in preventing and reducing acute and chronic neurotoxicity induced by oxaliplatin in colorectal cancer chemotherapy. This is the first systematic review and meta-analysis to address this question.

2. Method

2.1. Search strategy and selection criteria

A comprehensive literature search was performed using Medline, Embase, Cochrane Library and Google Scholar database up to 1st August 2011. Keywords for the search were: calcium, magnesium and oxaliplatin. The citations of all review articles and original articles were perused manually for additional articles. We also searched the annual meetings of the American Society of Clinical Oncology for available abstracts. Both fully published papers and abstracts were included and no limitation for language.

Studies have to satisfy the following criteria in order to be included in our review. All comparative randomised controlled trials (RCTs) and observational studies (case control or cohort) assessing infusion of Ca/Mg versus non-Ca/Mg in patients receiving oxaliplatin-based chemotherapy for colorectal cancer were included. Studies were excluded from our study if there were not enough published data for calculating an estimate of relative risk (RR) or odds ratio (OR) and their 95% confidence intervals (CIs). If there was more than one report relating to the same trial, the most recent or most informative was included.

We did not evaluate the quality score of the included studies because quality scoring of RCTs and observational studies in meta-analysis is varied and inconclusive[11,12] and may not be related to quality.[13] Instead, we listed the information of study design and performed stratified analysis.

2.2. Data extraction

Two reviewers screened the data independently. The following data were extracted from each study: basic information of the study (authors, year, location, study design information and patients' characteristics), treatments (oxaliplatin chemotherapy and Ca/Mg treatments) and relevant outcomes (toxicity grades, grade criteria and response rate). OR (RR) and 95%CIs were calculated by establishing 2×2 contingency tables based on the number of patients with incident neurotoxicity in each study. Disagreements were resolved by consensus among all authors.

2.3. Statistical analysis

We conducted subgroup meta-analysis on the basis of types of neurotoxicity grade criteria. The OR for neurotoxicity and RR for tumour response rate were calculated using STATA software 11.0 version (Stata Corporation, College Station, TX, USA). OR represents the odds of a neurotoxicity event occurring in the Ca/Mg+ group compared with the Ca/Mg− group. An $OR > 1$ indicates more toxicity in the Ca/Mg chemotherapy arm, and vice versa. We were unable to adjust ORs because they were calculated from raw data of the original trials. Statistical heterogeneity was measured using Cochran's Q test with a .10 level of significance. We also calculate I^2 statistic. If there was no heterogeneity, the fixed- and the random-effects models